Efficacy of Sacituzumab Govitecan (SG) in Locally Advanced (LA) or Metastatic Urothelial Cancer (mUC) by Trophoblast Cell Surface Antigen 2 (Trop-2) Expression

Yohann Loriot,[1] Arjun V. Balar,[2] Daniel P. Petrylak,[3] Arash Rezazadeh Kalebasty,[4] Petros Grivas,[5] Aude Fléchon,[6] Rohit K. Jain,[7] Neeraj Agarwal,[8] Manojkumar Bupathi,[9] Philippe Barthélémy,[10] Philippe Beuzeboc,[11] Phillip Palmbos,[12] Christos E. Kyriakopoulos,[13] Damien Pouessel,[14] Cora N. Sternberg,[15] Julia Tonelli,[16] Emon Elboudwarej,[16] Lauri Diehl,[16] Juliane M. Jürgensmeier,[16] Scott T. Tagawa[15]

[1]Institut de Cancérologie Gustave Roussy, Villejuif, France; [2]Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [3]Smilow Cancer Center, Yale School of Medicine, New Haven, CT, USA; [4]University of California Irvine, Irvine, CA, USA; [5]University of Washington, Fred Hutchinson Cancer Center, Seattle, WA, USA; [6]Centre Léon Bérard, Lyon, France; [7]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [8]Huntsman Cancer Hospital, Salt Lake City, UT, USA; [9]Rocky Mountain Cancer Centers, Littleton, CO, USA; [10]Hôpitaux Universitaires de Strasbourg/ Institut de Cancérologie Strasbourg Europe, Strasbourg, France; [11]Hôpital Foch, Suresnes, France; [12]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; [13]University of Wisconsin Carbone Cancer Center, Madison, WI, USA; [14]Institut Claudius Regaud/IUCT-Oncopole, Toulouse, France; [15]Weill Cornell Medicine, New York, NY, USA; [16]Gilead Sciences, Inc., Foster City, CA, USA

Poster 4579

TROPHY-U-01

Electronic copy of poster

Supplemental materials

Key Findings

- This analysis of Trop-2 expression in archival tumor samples collected from patients enrolled in TROPHY-U-01 showed that Trop-2 is highly expressed in UC
- No difference in ORR was observed with different Trop-2 expression (median/tertiles)
- PFS and OS for patients above and below Trop-2 median (or by tertile cut) were comparable within each cohort, using H-scores or percentage membrane positivity

Conclusions

- This analysis demonstrated efficacy benefit with SG alone or in combination with pembrolizumab in mUC, regardless of Trop-2 expression
- Additional studies are ongoing to confirm our findings in other datasets
  - TROPHY-U-01 study is currently enrolling patients in C4-6 in first-line therapy
  - The phase 3 TROPiCS-04 study has completed accrual and the results are pending

References: **1.** Koshkin VS, et al. *Transl Androl Urol*. 2021;10:4022-4035. **2.** National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 2.2023. **3.** Bahlinger V, et al. Poster presented at ASCO GU; Feb 16-18, 2023; San Francisco, CA. **4.** Rugo HS, et al. *Future Oncol*. 2020;16:705-715. **5.** Cardillo TM, et al. *Bioconjugate Chem*. 2015;26:919-931. **6.** Goldenberg DM, et al. *Expert Opin Biol Ther*. 2020;20:871-885. **7.** TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Gilead Sciences, Inc., Foster City, CA; 2023. **8.** Tagawa ST, et al. *J Clin Oncol*. 2021;39:2474-2485. **9.** Petrylak DP, et al. Oral presentation presented at ASCO GU; Feb 16-18, 2023; San Francisco, CA. **10.** Grivas P, et al. Poster presented at ASCO GU; Feb 16-18, 2023; San Francisco, CA.

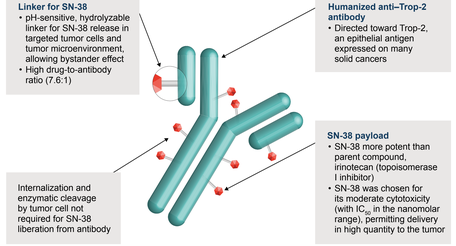
Acknowledgments: We thank the patients and their caregivers for helping us realize the possibilities of this research. We thank the dedicated clinical trial investigators and their devoted team members for participating in TROPHY-U-01. This study is sponsored by Gilead Sciences, Inc. Editorial support was provided by Priya Talluri, MSc, of Parexel and funded by Gilead Sciences, Inc.

Correspondence: stt2007@med.cornell.edu

Background

- Patients with locally advanced (LA) or metastatic urothelial cancer (mUC) who progress after platinum (PT)-based and checkpoint inhibitor (CPI) therapies have limited therapeutic options and an overall poor prognosis, emphasizing the need for new treatments[1,2]
- Human trophoblast cell surface antigen 2 (Trop-2) is a 40-kDa transmembrane glycoprotein encoded by the *TACSTD2* gene and is widely expressed in UC, representing a suitable target for treatment with an anti–Trop-2 antibody[3]
- Sacituzumab govitecan (SG) is an antibody-drug conjugate composed of an antibody targeting Trop-2 coupled to cytotoxic SN-38 payload through a hydrolysable linker (Figure 1)[4-7]
- SG received an accelerated US FDA approval for patients with unresectable, LA or mUC who had previously received PT therapy and a CPI based on the pivotal TROPHY-U-01 phase 2 study[7-10]:
  - Cohort 1 (C1; 113 patients with mUC who had progressed after PT-based therapy and CPI) had a 27% objective response rate (ORR); Cohort 2 (C2; 38 patients with mUC who were ineligible for PT-based therapy and progressed after CPI therapy) had a 32% ORR; and Cohort 3 (C3; 41 patients with mUC who progressed after PT-based therapy) had a 41% ORR

Figure 1. Sacituzumab govitecan, antibody-drug conjugate[3,7]



IC_{50}, half-maximal inhibitory concentration; Trop-2, trophoblast cell surface antigen 2.
Adapted from Rugo HS, et al. TROPICS-02: a phase III study investigating sacituzumab govitecan in the treatment of HR+/HER2- metastatic breast cancer. *Future Oncol*. 2020;16:705-715. Complete licensing info can be found here: http://creativecommons.org/licenses/by-nc-nd/4.0/.

Objective

- The objective of this analysis was to evaluate the potential impact of Trop-2 expression on efficacy outcomes in patients treated with SG in C1-3 of the TROPHY-U-01 study

Methods

- Patients received SG (10 mg/kg intravenous) on day 1 and day 8 of 21-day cycles; C3 patients also received pembrolizumab (200 mg) on day 1 of 21-day cycles. The primary end point was ORR by independent review. For details on the clinical study, refer to previous publications[8-10]
- Archival tumor samples collected at enrollment were assessed for Trop-2 protein expression using the SP295 anti–Trop-2 antibody immunohistochemistry (IHC; Roche Tissue Services) assay with assessment by:
  - Histological scores (H-scores; scale, 0-300)
  - Percentage of membrane-positive tumor cells (4× magnification)
- Trop-2 association with clinical end points was evaluated using unstratified Cox proportional hazards models for survival data and logistic regression for ORR
  - ORR was calculated by adding complete response and partial response (CR + PR) and dividing by the number of evaluable patients
- For progression-free survival (PFS) and overall survival (OS), Trop-2 data are displayed either as above/below median or by tertiles. Tertiles were determined by placing a similar number of patients in each tertile of Trop-2 expression using C1-3. Tertile categories are reported for C1 only, due to small sample sizes in C2 and C3

Results

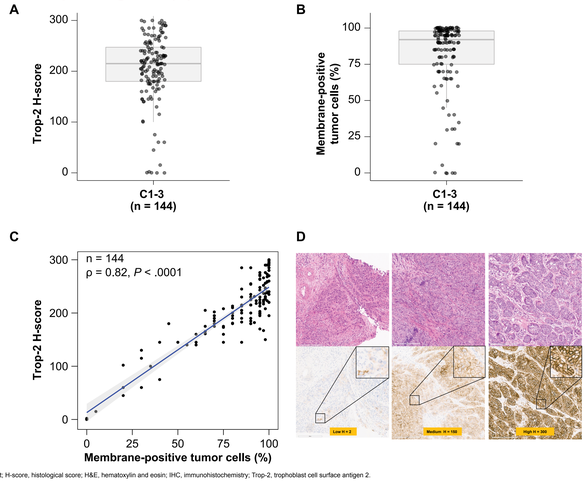
Patients

- At data cutoff, 192 patients were enrolled in C1-C3
  - 144 (75%) patients had tumor tissue samples evaluable for Trop-2 testing
  - 139 (72%) patients were evaluable for efficacy analysis based on Trop-2 expression
- Baseline characteristics for patients with Trop-2 data were consistent with the overall population

Trop-2 expression

- Trop-2 was highly expressed in tumor tissue samples from patients enrolled in the TROPHY study, in line with published data[5] (Figure 2)
- Median Trop-2 H-score and percentage of Trop-2 membrane–positive tumor cells for evaluable patient samples were 215 (180-247) and 92% (75-98), respectively
- These readouts were highly correlated (ρ = 0.82, $P < .0001$). Correlations with efficacy were therefore only performed using H-scores

Figure 2. Trop-2 H-score in C1-3 (A), percent Trop-2 membrane–positive tumor cells (B), correlation of both scoring metrices (C), examples for Trop-2 IHC images with corresponding H&E (D)



C, Cohort; H-score, histological score; H&E, hematoxylin and eosin; IHC, immunohistochemistry; Trop-2, trophoblast cell surface antigen 2.

No association between overall response rate (ORR) and Trop-2 expression

- ORR was not associated with Trop-2 expression, and response to SG was observed across all Trop-2 expression groups (Table 1)

Table 1. ORR in C1-3 by Trop-2 H-score (above vs below median)

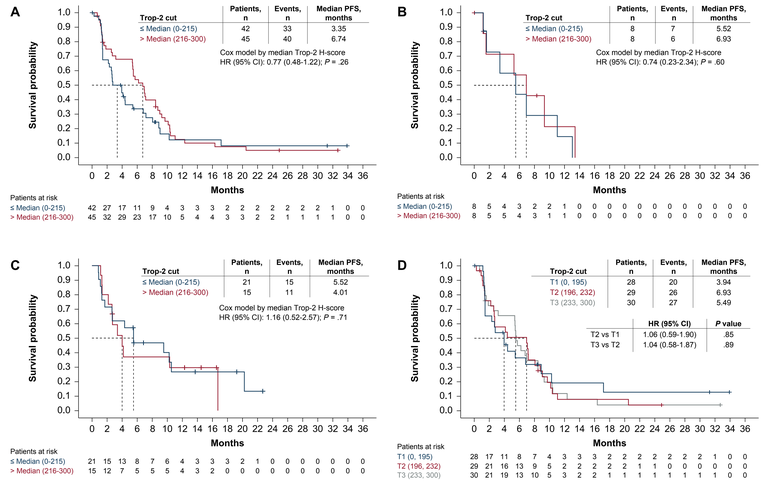
		≤ Median (0-215)		> Median (216-300)		Unadjusted (> med vs ≤ med)	
	N	CR + PR (%)	SD + PD (%)	CR + PR (%)	SD+ PD (%)	OR (95%CI)	*P* value
C1	87	12/42 (29)	30/42 (71)	16/45 (36)	29/45 (64)	1.38 (0.56-3.41)	.49
C2	16	3/8 (37.5)	5/8 (62.5)	3/8 (37.5)	5/8 (62.5)	1.00 (0.13-7.57)	1.00
C3	36	10/21 (48)	11/21 (52)	6/15 (40)	9/15 (60)	0.73 (0.19-2.81)	.65

C, Cohort; CI, confidence interval; CR, complete response; H-score, histological score; med, median; OR, odds ratio; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; Trop-2, human trophoblast cell surface antigen 2.

PFS and OS in C1-3 by Trop-2 H-score (median and tertile cut)

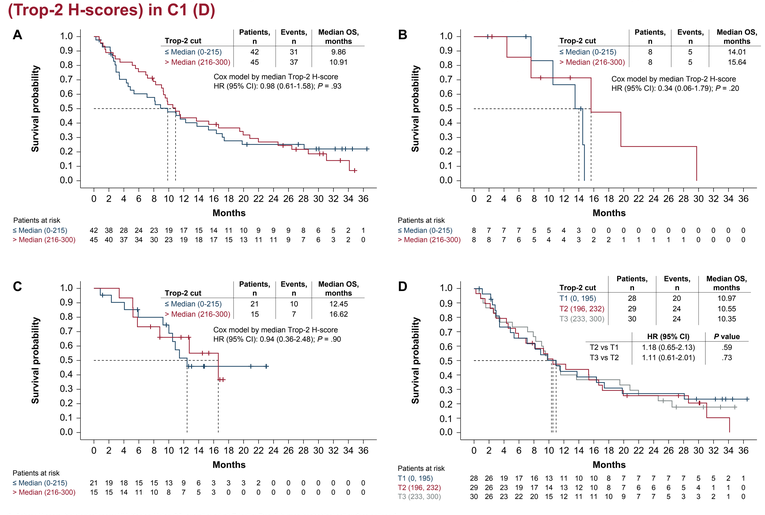
- There was no statistically significant relationship between Trop-2 and PFS, regardless of how Trop-2 was categorized (Figure 3)
- There was no statistically significant relationship between Trop-2 and OS, regardless of how Trop-2 was categorized (Figure 4)

Figure 3. KM estimates of PFS by median Trop-2 H-scores in C1 (A), C2 (B), C3 (C), and by tertiles (Trop-2 H-scores) in C1 (D)



C, Cohort; H-score, histological score; KM, Kaplan-Meier; PFS, progression-free survival; T, tertile; Trop-2, human trophoblast cell surface antigen 2.

Figure 4. KM estimates of OS by median Trop-2 H-scores in C1 (A), C2 (B), C3 (C), and by tertiles (Trop-2 H-scores) in C1 (D)



C, Cohort; H-score, histological score; KM, Kaplan-Meier; OS, overall survival; T, tertile; Trop-2, human trophoblast cell surface antigen 2.